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Tricyclic Antidepressant Amitriptyline Suppresses Ca^{2+} Responses in Rat Peritoneal Macrophages

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Abstract—Amitriptyline is a tricyclic antidepressant widely used in clinical practice for the treatment of anxiety and depression and chronic pain. These drugs have a multifaceted effect on cellular processes. One of their targets is sigma-1 receptors. Sigma-1 receptors are molecular chaperones located in the membrane of the endoplasmic reticulum; they are characterized by a unique structure and pharmacological profile. Sigma-1 receptors regulate many cellular processes in health and disease, including processes of Ca^{2+} signaling. Using Fura-2AM fluorescent Ca^{2+} probe, we showed for the first time that sigma-1 receptor agonist, the antidepressant amitriptyline, significantly suppresses Ca^{2+} mobilization from the intracellular Ca^{2+} stores and subsequent store-dependent Ca^{2+} entry into cells caused by inhibitors of endoplasmic Ca^{2+} ATPases thapsigargin and cyclopiazonic acid, as well as the disulfide-containing immunomodulators glutoxim and molixan, in rat peritoneal macrophages. The results indicate the participation of sigma-1 receptors in the complex signaling cascade caused by glutoxim or molixan, leading to an increase in intracellular Ca^{2+} concentration in macrophages. Data also indicate that sigma-1 receptors participate in the regulation of store-dependent Ca^{2+} entry in macrophages.

Keywords: amitriptyline, sigma-1 receptors, peritoneal macrophages, intracellular Ca^{2+} concentration

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Amitriptyline—(5-(3-dimethylaminopropylidene)-10,11-dihydrodibenzocycloheptene)—is one of the main representatives of tricyclic antidepressants, which are widely used in clinical practice for the treatment of anxiety and depressive conditions (Gillman, 2007; Danilov, 2019) and various types of chronic pain (neuralgia, diabetic neuropathies, etc.) (Rico-Villademoros et al., 2015; Lawson, 2017; Belinskaia et al., 2019; Cardoso et al., 2022). These antidepressants are known to have a multifaceted influence on cellular processes.

The variety of effects of amitriptyline, like other tricyclic antidepressants, may be due to it's amphiphilic properties. Like other amphiphilic substances, it effectively penetrates membranes and can be incorporated into the inner monolayer of the membrane, enriched in anionic lipids (primarily phosphoinositides) (Oruch et al., 2010). Therefore, amitriptyline may be involved in the regulation of signaling processes and intracellular transport. Thus, the affinity of antidepressants for sigma-1 receptors has been revealed (Weber et al., 1986; Narita et al., 1996; Fishback et al., 2010; Hayashi et al., 2011; Wang et al., 2016; 2022).

Sigma-1 receptors, which have a unique history, structure and pharmacology, regulate many cellular processes, both normally and in pathology (Rousseaux and Greene, 2016; Su et al., 2016; Schmidt and Kruse, 2019; Pergolizzi et al., 2023). These receptors are multifunctional molecular chaperones located in the membrane of the endoplasmic reticulum in areas bordering mitochondria (Su et al., 2010; Delprat et al., 2020; Aishwarya et al., 2021; Munguia-Galaviz et al., 2023). In addition, they can translocate to the plasmalemma and interact with other receptors and ion channels, and they are also found in the nuclear envelope, where they participate in transcription regulation (Su et al., 2016). Sigma-1 receptors are expressed in a wide range of cells, including immune cells (Penke et al., 2018; Pergolizzi et al., 2023).

One of the unique properties of sigma-1 receptors is their extremely broad pharmacological profile. The ligands of these receptors include compounds that differ in both their chemical structure and the mechanism of action on cells: antidepressants (fluvoxamine, fluoxetine, sertraline, imipramine, amitriptyline), antipsychotics (haloperidol, chlorpromazine), analgesics (pentazocine), anxiolytics (afobazole), anticonvulsants (phenytoin), antitussives (dextromethorphan, carbetapentane), and antihistamine (chlorphenamine) drugs, narcotic drugs (metha-

mphetamine and cocaine), and drugs used in the treatment of neurodegenerative diseases (amantadine, memantine, donepezil) (Werling et al., 2007; Cobos et al., 2008; Chu and Ruoho, 2016; Voronin et al., 2020).

By interacting with target proteins, sigma-1 receptors regulate many cellular processes in health and disease, including Ca^{2+} signaling (Schmidt and Kruse, 2019; Pontisso, Combettes, 2021). In the plasma membrane, sigma-1 receptors interact with voltage-gated Ca^{2+}, Na^+, and K^+ channels, proton-activated ion channels (ASICs); TRPA1, TRPV1, and TRPM8 Ca^{2+}-permeable channels; NMDA receptors; G-protein coupled receptors (muscarinic acetylcholine receptors; μ-opioid and D1- and D2-dopamine receptors); and receptor tyrosine kinases and other target proteins (Su et al., 2010, 2016; Ortiz-Renteria et al., 2018; Cortés-Montero et al., 2019; Morales-Lázaro et al., 2019; Schmidt and Kruse, 2019; Munguia-Galaviz et al., 2023). In the membrane of the endoplasmic reticulum, the sigma-1 receptor interacts with the type 3 inositol-1,4,5-triphosphate receptor, another molecular chaperone protein BiP (binding immunoglobulin protein) (Hayashi and Su, 2007), and the Ca^{2+} sensor protein STIM1 (Srivats et al., 2016). It is known that the interaction of sigma-1 receptors with inositol 1,4,5-trisphosphate receptors regulates both phases of Ca^{2+} response: Ca^{2+} mobilization from the stores (Hayashi et al., 2000; Wu and Bowen, 2008) and Ca^{2+} entry from the external medium (Hayashi and Su, 2007; Pontisso and Combettes, 2021). It has also been shown that sigma-1 receptors are also involved in the regulation of store-dependent Ca^{2+} entry into cells of different types (Brailoiu et al., 2016; Srivats et al., 2016).

Previously, we were the first to show that ligands of sigma-1 receptors, typical first-generation antipsychotics haloperidol (a butyrophenone derivative) (Krutetskaya et al., 2017, 2018) and the phenothiazine derivatives chlorpromazine and trifluoperazine (Milenina et al., 2022), significantly suppress in rat peritoneal macrophages both phases of Ca^{2+} responses caused by two types of agents: the disulfide-containing immunomodulators glutoxim® (disodium salt of oxidized glutathione with d-metal in nanoconcentration) and molixan® (complex of glutoxim and inosine nucleoside), as well as inhibitors of endoplasmic Ca^{2+} ATPases thapsigargin and cyclopiazonic acid (CPA).

To confirm that sigma-1 receptors participate in the regulation of the processes of Ca^{2+} signaling in macrophages, and also taking into account the important role of sigma-1 receptors in the pathogenesis of depressive states (Voronin et al., 2020; Wang et al., 2022), it seemed appropriate to study the effect of the sigma-1 receptor agonist—the tricyclic antidepressant amitriptyline (Villard et al., 2011; Rousseaux and Greene, 2016; Wang et al., 2016; Penke et al., 2018)—on Ca^{2+} responses induced by glutoxim and molixan, as well as thapsigargin and CPA in rat peritoneal macrophages. This was the subject of this study.

MATERIALS AND METHODS

Isolation and Cultivation of Rat Peritoneal Macrophages

Experiments were performed on cultured resident peritoneal macrophages of Wistar rats.

Macrophages were isolated from the peritoneal cavity of rats using the traditional method (Conrad, 1981). The weight of the rats was 180–250 g. Immediately after isolation, the cells had a spherical shape (diameter 10–20 μm). A suspension of macrophages was placed in culture dishes with 10 × 10-mm quartz glasses and cultured for 1–3 days at a temperature of 37°C in medium 199 (pH 7.2). The medium contained 20% bovine serum, glutamine (3%), penicillin (100 U/mL), and streptomycin (100 mg/mL). The α-naphthyl esterase test showed that at least 96% of the cells in the monolayers were macrophages (Monahan et al., 1981).

Experiments were carried out 1–2 days after the start of cell cultivation at a temperature of 22–24°C. The experimental chamber was filled with a physiological solution of the following ionic composition (mM): 140 NaCl, 5 KCl, 1 $CaCl_2$, 1 $MgCl_2$, and 5 HEPES-NaOH, pH 7.3–7.4. In the case of using a calcium-free medium, the solution contained 0 mM $CaCl_2$ and 1 mM EGTA. Quartz glasses with cells were placed in an experimental chamber.

Measurement of Intracellular Ca^{2+} Concentration ($[Ca^{2+}]_i$)

The Fura-2AM fluorescent probe (Sigma-Aldrich, United States) was used. Cells were placed in a physiological solution containing 2 μM Fura-2AM and incubated for 45 min at 22–24°C. Then, the glasses with stained cells were transferred to the experimental chamber fixed on the table of Leica DM 4000B fluorescent microscope (Leica Microsystems, Germany). Fluorescence of the object was excited through a microscope objective at wavelengths of 340 and 380 nm. The corresponding parts of the spectrum were isolated using narrow-band optical filters. Emission was recorded at a wavelength of 510 nm using a specialized Leica DFC340FX video camera. The experiment was controlled using the ImageJ image processing system (Micro-Manager 1.4 plugin).

The measurement result was the ratio of the fluorescence intensities of Fura-2AM when irradiated with light with a wavelength of 340 nm to the fluorescence intensity when irradiated with light with a wavelength of 380 nm (F_{340}/F_{380}), reflecting changes in $[Ca^{2+}]_i$ in cells during measurements (Xie et al., 2002). Measurements were carried out every 20 s, irradiating the object for 2 s to avoid photobleaching. A 10×

objective with an aperture of 8 mm was used. $[Ca^{2+}]_i$ values were calculated using the Grynkiewicz equation (Grynkiewicz et al., 1985). For statistical analysis, we used Student's *t*-test. Data are presented as mean and standard deviation. Each registration was obtained for a group of 40–50 cells. The figures show the results of similar experiments from six to eight independent ones. The differences were considered significant at $p \le 0.05$.

Reagents Used

Reagents from Sigma-Aldrich (United States) were used. Stock solutions of Fura-2AM (1 mM), CPA (10 mM), and thapsigargin (0.5 mM) were prepared in dimethyl sulfoxide. The drugs glutoxim and molixan were provided by PHARMA-VAM (St. Petersburg). Stock solutions of glutoxim (50 mg/mL), amitriptyline (20 mg/mL) and molixan (50 mg/mL) were prepared in water.

RESULTS AND DISCUSSION

The Effect of Amitriptyline on Ca^{2+} Responses Induced by Disulfide-Containing Immunomodulators

Glutoxim and molixan, pharmacological analogues of oxidized glutathione, are used as cytoprotectors and immunomodulators in the treatment of viral, bacterial, and oncological diseases (Borisov et al., 2001; Antushevich et al., 2013; Tolstoy et al., 2019). It is known that they influence redox regulation processes in cells, but the biophysical mechanism of their action is not fully understood. Research in recent years has shown that molixan may be useful in the treatment or prevention of COVID-19 coronavirus infection, as it accelerates the transition of the disease to a milder form (Dubina et al., 2021). Previously (Kurilova et al., 2008, 2012), we were the first to discover that glutoxim and molixan induce a biphasic Ca^{2+} response in rat peritoneal macrophages—Ca^{2+} mobilization from the thapsigargin-sensitive Ca^{2+} stores and subsequent store-dependent Ca^{2+} entry.

In control experiments, it was found that a 20-min incubation of macrophages in a calcium-free medium with 100 μg/mL glutoxim (Fig. 1a) or 100 μg/mL molixan (Fig. 2a) is accompanied by a slowly growing increase in $[Ca^{2+}]_i$, reflecting the Ca^{2+} mobilization from the intracellular Ca^{2+} stores. On average, 20 min after the addition of glutoxim or molixan, $[Ca^{2+}]_i$ increased from a basal level of 90 ± 18 to 150 ± 19 nM ($n = 6$; $p < 0.05$) for glutoxim and 158 ± 20 nM ($n = 6$; $p < 0.05$) for molixan. With the subsequent addition of 2 mM Ca^{2+} to the external medium, a further increase in $[Ca^{2+}]_i$ was observed, corresponding to the store-dependent Ca^{2+} entry into macrophages (Figs. 1, 2). The $[Ca^{2+}]_i$ increase during Ca^{2+} entry averaged 382 ± 32 ($n = 6$; $p < 0.05$) for glutoxim and 394 ± 34 nM ($n = 6$; $p < 0.05$) for molixan.

It was shown for the first time that a 20-min preincubation of macrophages with 20 μg/mL amitriptyline caused significant suppression of Ca^{2+} mobilization from the stores (by 39.6 ± 9.2%, $n = 7$; $p < 0.05$) and store-dependent Ca^{2+} entry into macrophages (by 46.3 ± 10.1%, $n = 7$; $p < 0.05$), induced by 100 μg/mL glutoxim (Fig. 1b). Similar results were obtained in experiments on the effect of 20 μg/mL amitriptyline on Ca^{2+} responses induced by 100 μg/mL molixan (Fig. 2b). Thus, amitriptyline caused suppression of Ca^{2+} mobilization from the stores by 46.8 ± 8.2% ($n = 7$; $p < 0.05$) and suppression of store-dependent Ca^{2+} entry into cells by 55.4 ± 9.0% ($n = 7$; $p < 0.05$), induced by molixan.

In addition, we have shown that the addition of 40 μg/mL amitriptyline during glutoxim-induced (Fig. 1a) or molixan-induced (Fig. 2a) developed Ca^{2+} entry, significantly (by 67.8 ± 15.0%, $n = 12$; $p < 0.05$) suppresses store-dependent Ca^{2+} entry into macrophages.

The Effect of Amitriptyline on Ca^{2+} Responses Induced by Inhibitors of Endoplasmic Ca^{2+}- ATPases

In control experiments, it was shown that 0.5 μM thapsigargin, added to macrophages in a calcium-free medium, causes a slight increase in $[Ca^{2+}]_i$ relative to the basal level (on average, by 35 ± 9 nM, $n = 10$; $p < 0.05$). This increase in $[Ca^{2+}]_i$ is mediated by Ca^{2+} mobilization from intracellular Ca^{2+} stores (Fig. 3a). Upon further addition of 2 mM Ca^{2+} to the external medium, store-dependent Ca^{2+} entry into macrophages was observed (Fig. 3a). The increase in $[Ca^{2+}]_i$ during Ca^{2+} entry averaged 175.1 ± 23.2 nM ($n = 10$; $p < 0.05$). When using 10 μM CPA (Fig. 4a), similar results were obtained: Ca^{2+} mobilization from the stores averaged 29.8 ± 9.2 nM ($n = 7$; $p < 0.05$), and Ca^{2+} entry into macrophages was 143.3 ± 21.4 nM ($n = 7$; $p < 0.05$) (Fig. 4a).

It was discovered for the first time that preincubation of cells with 20 μg/mL amitriptyline in a calcium-free medium for 20 min leads to suppression of both phases of Ca^{2+}-responses induced by 0.5 μM thapsigargin (Fig. 3*b*). The suppression of Ca^{2+} mobilization from the stores was 21.3 ± 5.1% ($n = 7$; $p < 0.05$), and the store-dependent Ca^{2+} entry was 47.9 ± 11.4% ($n = 7$; $p < 0.05$). When using 10 μM CPA, similar results were obtained (Fig. 4b). Amitriptyline suppressed Ca^{2+} mobilization from the stores by 20.6 ± 6.2% ($n = 7$; $p < 0.05$) and store-dependent Ca^{2+} entry by 42.9 ± 10.4% ($n = 7$; $p < 0.05$). This indicates the participation of sigma-1 receptors in the activation of store-dependent Ca^{2+} entry into macro-

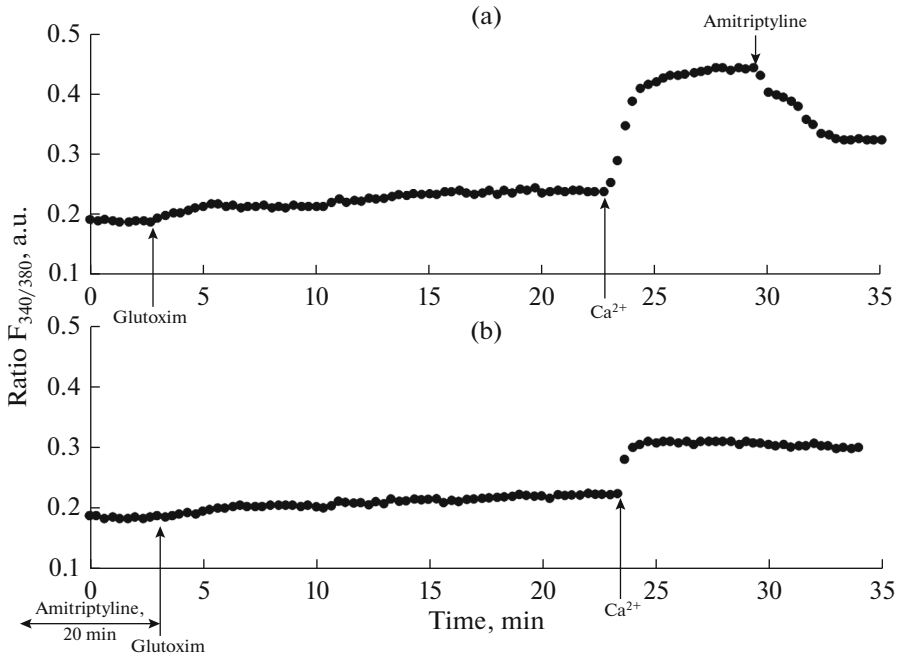

Fig. 1. The effect of amitriptyline on the $[Ca^{2+}]_i$ increase induced by glutoxim in rat peritoneal macrophages. Here and in Figs. 2–4, the ratio of fluorescence intensities of Fura-2AM at excitation wavelengths of 340 and 380 nm (F_{340}/F_{380}) is *along the ordinate axis*. (a) Macrophages were incubated for 20 min in the presence of 100 μg/mL glutoxim in a nominally calcium-free medium; then, Ca^{2+} entry was initiated by introducing 2 mM Ca^{2+} into the external medium; against the background of the developed Ca^{2+} entry, 40 μg/mL amitriptyline was added; (*b*) macrophages in a calcium-free medium were incubated for 20 min with 20 μg/mL amitriptyline; then, 100 μg/mL glutoxim was added, and, after 20 min, Ca^{2+} entry was initiated by introducing 2 mM Ca^{2+} into the external medium. Here and in Figs. 2–4 each recording was obtained for a group of 40–50 cells and represents a typical variant of from six to eight independent experiments.

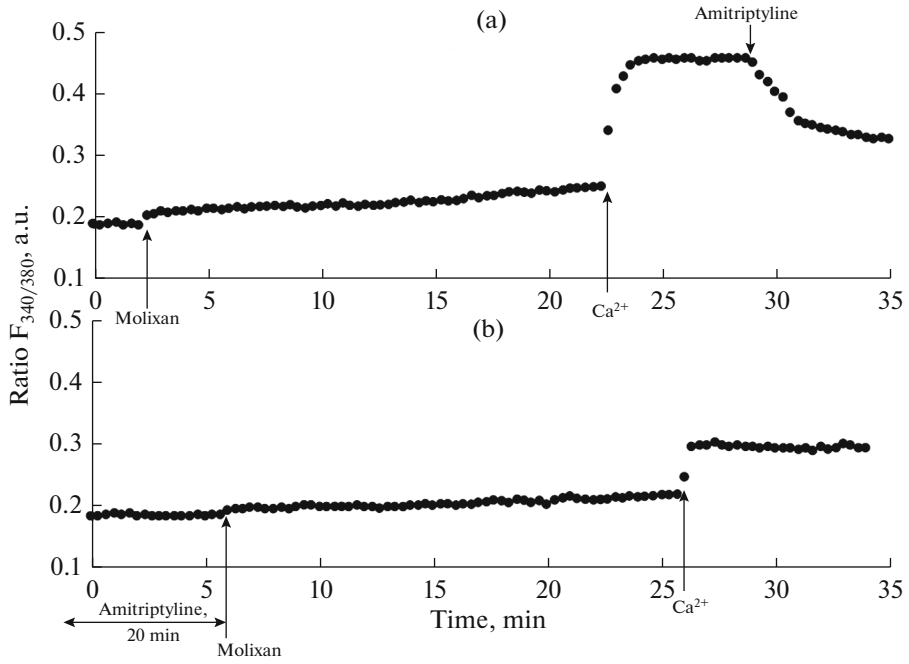

Fig. 2. The effect of amitriptyline on the $[Ca^{2+}]_i$ increase induced by molixan in rat peritoneal macrophages. (a) Macrophages were incubated for 20 min in the presence of 100 μg/mL molixan in a nominally calcium-free medium; then, Ca^{2+} entry was initiated by introducing 2 mM Ca^{2+} into the external medium; against the background of the developed Ca^{2+} entry 40 μg/mL amitriptyline was added; (b) macrophages in a calcium-free medium were incubated for 20 min with 20 μg/mL amitriptyline; then, 100 μg/mL molixan was added, and, after 20 min, Ca^{2+} entry was initiated by introducing 2 mM Ca^{2+} into the external medium.

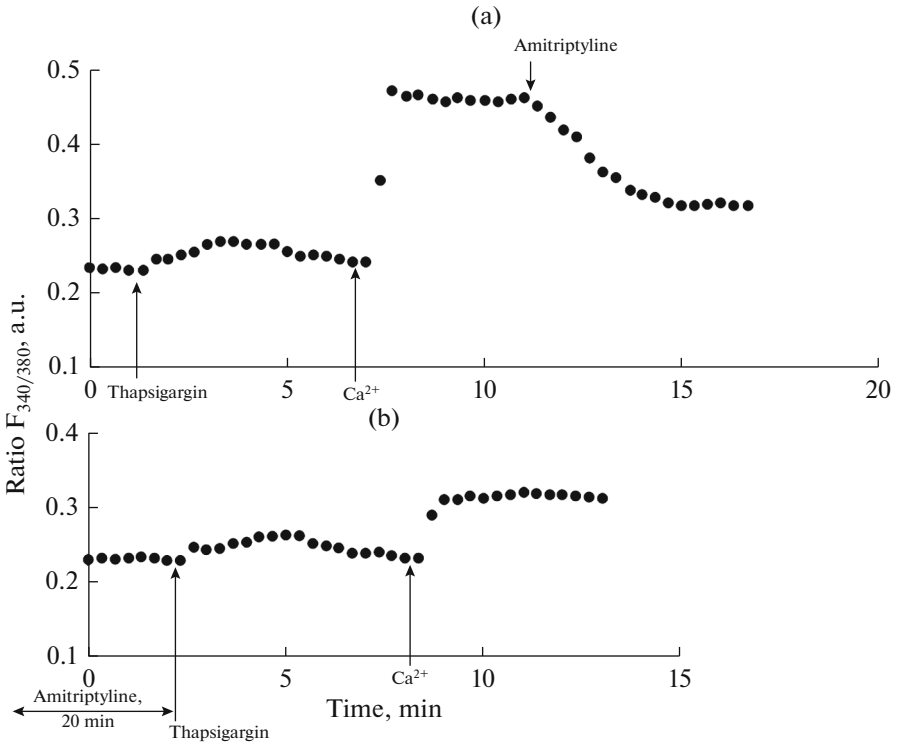

Fig. 3. The effect of amitriptyline on Ca^{2+} responses induced by thapsigargin in rat peritoneal macrophages. (a) Macrophages were stimulated with 0.5 μM thapsigargin in a nominally calcium-free medium; then, Ca^{2+} entry was initiated by introducing 2 mM Ca^{2+} into the external medium; against the background of the developed Ca^{2+} entry, 40 μg/mL amitriptyline was added; (b) macrophages were preincubated for 20 min with 20 μg/mL amitriptyline in a calcium-free medium; then, 0.5 μM thapsigargin was added, after which Ca^{2+} entry was initiated by introducing 2 mM Ca^{2+} into the external medium.

phages, induced by endoplasmic Ca^{2+} ATPases inhibitors.

It was also shown that administration of 40 μg/mL amitriptyline during thapsigargin-induced (Fig. 3a) or CPA-induced (Fig. 4a) developed Ca^{2+} entry significantly (by 50.5 ± 14.3%, $n = 12$; $p < 0.05$) suppresses store-dependent Ca^{2+} entry into macrophages. This indicated the participation of sigma-1 receptors in the maintenance of the store-dependent Ca^{2+} entry into macrophages.

Thus, in this work, we have shown for the first time that sigma-1 receptor agonist, the tricyclic antidepressant amitriptyline, suppresses both phases of Ca^{2+} responses induced by glutoxim or molixan, as well as thapsigargin and CPA, in peritoneal macrophages. The data obtained are consistent with the results of other researchers. Thus, it was found that amitriptyline inhibits Ca^{2+} mobilization from the stores and the store-dependent Ca^{2+} entry induced by ATP or thapsigargin in human leukemia cells (HL-60 line) (Harper and Daly, 1999). The sigma-1 receptor agonist cocaine has also been shown to suppress thapsigargin-induced store-dependent Ca^{2+} entry in endothelial cells of rat brain vessels (Brailoiu et al., 2016), and the compound (+)-SKF-10047, also an agonist of sigma-1 receptors, inhibits Ca^{2+} mobilization from the stores and the store-dependent Ca^{2+} entry induced by thapsigargin in Chinese hamster oocytes and human embryonic kidney cells (HEK 293 line) (Srivats et al., 2016).

Amitriptyline is also known to inhibit voltage-gated Ca^{2+} channels in cells of various types. Thus, amitriptyline inhibits voltage-dependent Ca^{2+}-channels in rat brain synaptosomes (Lavoie et al., 1990), reversibly and dose-dependently blocks L-type voltage-dependent Ca^{2+} channels (Cav1.2) in rat cardiac ventricular myocytes (Zahradnik et al., 2008), rat forebrain neurons (Bang et al., 2021), and mouse trigeminal ganglion neurons (Wu et al., 2012), as well as N-type Ca^{2+} channels (Cav2.2) in neuroblastoma cells (SH-SY5Y line) (Cardoso et al., 2022). Another sigma-1 receptor agonist, compound (+)-SKF-10047, inhibits Ca^{2+} entry caused by KCl, and dose-dependently blocks L-type Ca^{2+} channels (Cav1.2) in rat retinal ganglion cells (RGC-5 line) (Tchedre et al., 2008). Sigma-1 receptor agonists (compounds SKF-10047 and Pre-084) also inhibit N-type Ca^{2+} channels (Cav2.2) in rat striatal neurons (Zhang et al., 2017). In addition, a specific sigma-1 receptor agonist, narcotic analgesic (+)-pentazocine, modulates all the biophysical characteristics of voltage-dependent Ca^{2+} channels of N , L, P/Q, and R types in rat sympathetic

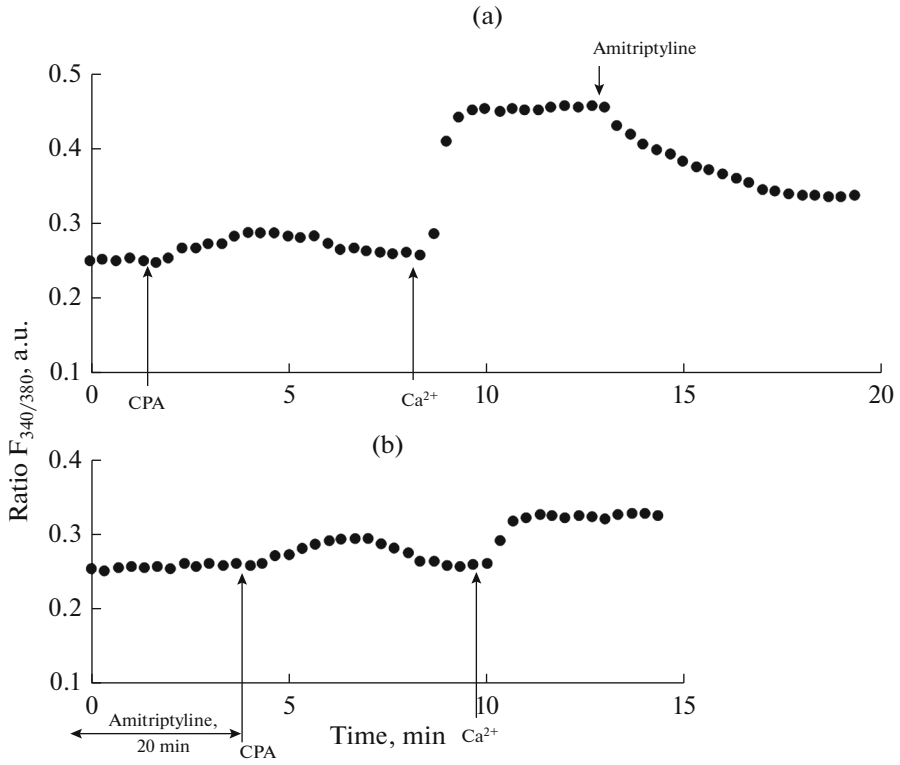

Fig. 4. The effect of amitriptyline on Ca^{2+} responses induced by cyclopiazonic acid (CPA) in rat peritoneal macrophages. (a) Macrophages were stimulated with 10 μM CPA in a nominally calcium-free medium, then Ca^{2+} entry was initiated by introducing 2 mM Ca^{2+} into the external medium; against the background of the developed Ca^{2+} entry, 40 μg/mL amitriptyline was added; (b) macrophages were preincubated for 20 min with 20 μg/mL amitriptyline in a calcium-free medium; then, 10 μM CPA was added, after which Ca^{2+} entry was initiated by introducing 2 mM Ca^{2+} into the external medium.

and parasympathetic neurons: it reversibly and dose-dependently reduces the peak amplitude of currents, accelerates the kinetics of inactivation and shifts the voltage dependence of activation and inactivation towards negative potentials (Zhang, Cuevas, 2002).

Amitriptyline also blocks Ca^{2+} entry via NMDA receptor channels (Stepanenko et al., 2019, 2022) and TRPC4 channels in human embryonic kidney cells (HEK 293 line) and mouse colon myocytes (Jeong et al., 2022).

The results of this and earlier works (Krutetskaya et al., 2017, 2018; Milenina et al., 2022) on the suppression by sigma-1 receptor ligands of Ca^{2+} responses caused by glutoxim and molixan in macrophages indicate the participation of sigma-1 receptors in glutoxim- or molixan-induced signaling cascade leading to an increase in $[Ca^{2+}]_i$ in rat peritoneal macrophages. The results also indicate that the use of glutoxim or molixan in combination with amitriptyline in clinical practice is undesirable.

In addition, the data obtained indicate the participation of sigma-1 receptors in the regulation of store-dependent Ca^{2+} entry caused by both disulfide-containing immunomodulators and inhibitors of endoplasmic Ca^{2+}-ATPases in rat peritoneal macrophages, which allows us to consider sigma-1 receptors as a new regulatory component of the signaling complex of store-dependent Ca^{2+} entry in macrophages. Sigma-1 receptors may influence store-dependent Ca^{2+} entry, regulating the binding of the main components of the store-dependent Ca^{2+} entry complex–STIM1 proteins in the membrane of the endoplasmic reticulum and Orai1 channels in the plasmalemma (Srivats et al., 2016).

The results may also contribute to a more detailed understanding of the molecular mechanisms of the pharmacological action of tricyclic antidepressants. In addition, the data obtained may be useful for the treatment of diseases associated with impaired functioning of sigma-1 receptors. Thus, it is known that changes in the subcellular localization, expression and signaling functions of sigma-1 receptors lead to the development of a wide range of human diseases (Aishwarya et al., 2021; Pergolizzi et al., 2023). The involvement of these receptors in the pathophysiology of neuropsychiatric diseases (schizophrenia, anxiety disorders, depressive states and dementia) (Tsai et al., 2014; Ren et al., 2022; Salaciak and Pytka, 2022), neurodegenerative diseases (Alzheimer's, Huntington's, and Parkinson's diseases, amyotrophic lateral sclerosis) (Ryskamp et al., 2019; Penke et al., 2018; Yang et al., 2019;

Herrando-Grabulosa et al., 2020; Zhemkov et al., 2021; Bogár et al., 2022; Lachance et al., 2023; Malar et al., 2023), oncological (Kim and Maher, 2017; Pontisso and Combettes, 2021) and cardiovascular (Munguia-Galaviz et al., 2023) diseases, as well as pain syndromes (Merlos et al., 2017a, 2017b) and retinopathy (Smith et al., 2018). This made it possible to consider sigma-1 receptors as promising pharmacological targets for the treatment of these diseases.

Recently, the possible role of sigma-1 receptors in the pathophysiology of coronavirus infection (COVID-19) has also been studied. There is evidence indicating that sigma-1 receptors may become one of the therapeutic targets in the treatment of coronavirus infection (Vela, 2020; Hashimoto, 2021). It is assumed that these receptors modulate host cell adaptive stress response mechanisms and are involved in the early stages of viral replication. Thus, it has been shown that the NSP6 protein of SARS-CoV-2 virus interacts with sigma-1 receptors, which play an important role in regulating endoplasmic reticulum stress (Gordon et al., 2020).

Many drugs that are repurposed to treat patients with COVID-19 are ligands for sigma-1 receptors. These include amitriptyline and other antidepressants (Vela, 2020; Hashimoto, 2021). There is evidence that cationic amphiphilic compounds, which include tricyclic antidepressants, have antiviral activity and inhibit the entry and replication of RNA viruses (Gitahy Falcao Faria et al., 2021). Thus, it has been shown that the tricyclic antidepressants amitriptyline and imipramine have significant antiviral activity and bind strongly to the S protein of the SARS-CoV-2 and MERS-CoV viruses and inhibit the replication of SARS-CoV-2 and MERS-CoV in monkey cells (VeroE6 line) (Kutkat et al., 2022). Another sigma-1 receptor agonist, the antidepressant fluvoxamine, modulates S protein endocytosis of SARS-CoV-2 virus in cells (line HEK 293) of the human embryonic kidney (Glebov, 2021).

Clinical trials have shown that the use of antidepressants in the early stages of COVID-19 reduces mortality and reduces the risk of requiring mechanical ventilation in patients with COVID-19 (Hashimoto et al., 2022; Mahdi et al., 2022; Mas et al., 2022; Zheng et al., 2022). It is believed that the most promising drug among antidepressants is sigma-1 receptor agonist fluvoxamine (Hashimoto et al. 2021, 2022; Sukhatme et al., 2021).

It was also discovered that another agonist of sigma-1 receptors, the antidepressant fluoxetine, inhibits SARS-CoV-2 (Zimniak et al., 2021; Fred et al., 2022), and it has passed clinical trials as a drug for the treatment of patients with COVID-19, reduces mortality, and reduces the risk of requiring mechanical ventilation in patients with COVID-19 (Hoertel et al., 2021).

One of the main symptoms of severe respiratory syndrome in patients who have had COVID-19 is headache. A clinical trial on 905 patients with COVID-19 showed amitriptyline to be effective for the treatment of patients with post-Covid headaches, including migraine (Gonzalez-Martinez et al., 2022).

In addition, amitriptyline has been shown to prevent SARS-CoV-2 infection of human adenocarcinoma cells (Caco-2 line), and treatment of volunteers with low concentrations of amitriptyline prevented infection with the S-protein of SARS-CoV-2 virus of freshly isolated human nasal epithelial cells (Carpinteiro et al., 2020).

It is also known that viruses, including SARS-CoV-2, have developed mechanisms to disrupt host cell Ca^{2+} homeostasis and increase $[Ca^{2+}]_i$, since Ca^{2+} is necessary for the virus to enter the cell and for its replication, maturation, and release (Zhoua et al. 2009; Chen et al., 2019; Jamison et al., 2022). In this regard, preventing virus-induced increase of $[Ca^{2+}]_i$ by inhibiting calcium release channels in the endoplasmic reticulum membrane (inositol-1,4,5-trisphosphate receptors and ryanodine receptors) or Ca^{2+} entry channels in the plasmalemma (voltage-dependent and store-dependent Ca^{2+} channels) is one of the approaches in the treatment of viral infections (Chen et al., 2019). Thus, it was found that the blockers of voltage-dependent Ca^{2+}-channels nifedipine and amlodipine reduce mortality and reduce the risk of requiring mechanical ventilation in elderly patients with COVID-19 and hypertension (Solaimanzadeh, 2020; Zhang et al., 2020). It has also been shown that intravenous administration of the blocker of store-dependent Ca^{2+} channels, compound Auxora, to patients with severe pneumonia due to COVID-19 stabilizes the lung endothelium and inhibits the release of pro-inflammatory cytokines, thereby significantly facilitating and accelerating the recovery of patients (Miller et al., 2020; Berlansky et al., 2022).

Thus, the results of this work on the suppression by the sigma-1 receptor agonist amitriptyline of both phases of Ca^{2+} responses induced by disulfide-containing immunomodulators and inhibitors of endoplasmic Ca^{2+}-ATPases in rat peritoneal macrophages, further confirm the versatility of the effects of tricyclic antidepressants and suggest their therapeutic potential as ligands of sigma-1 receptors.

ABBREVIATIONS AND NOTATION

$[Ca^{2+}]_i$	intracellular Ca^{2+} concentration
CPA	cyclopiazonic acid

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Medical University). No additional grants were received to conduct or direct this specific study were obtained.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Experiments on animals were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (http://oacu.od.nih.gov/regs/index.htm). The keeping of animals and all manipulations were carried out in accordance with regulatory documents and the requirements of Order of the Ministry of Health of Russia no. 267 of June 19, 2003, "On Approval of the Rules of Laboratory Practice in the Russian Federation." The study was approved by the Ethics Committee of St. Petersburg University (St. Petersburg, Russia), protocol no. 10 dated November 11, 2021.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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